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(54) Title: **NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN G PROTEIN-COUPLED RECEPTORS**

(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

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CLAIMS

What is claimed is:

1. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-3(F313K).
- 5 2. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 1.
3. A Plasmid comprising a Vector and the cDNA of claim 1.
4. A Host Cell comprising the Plasmid of claim 3.
5. A cDNA encoding a non-endogenous, constitutively activated version of a human
10 G protein-coupled receptor comprising hARE-4(V233K)
6. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 5.
7. A Plasmid comprising a Vector and the cDNA of claim 5.
8. A Host Cell comprising the Plasmid of claim 7.
- 15 9. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-5(A240K).
10. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 9.
11. A Plasmid comprising a Vector and the cDNA of claim 5.
- 20 12. A Host Cell comprising the Plasmid of claim 11.
13. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR14(L257K).

14. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 13.
15. A Plasmid comprising a Vector and the cDNA of claim 13.
- 5 16. A Host Cell comprising the Plasmid of claim 15.
17. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR27(C283K).
18. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 17.
- 10 19. A Plasmid comprising a Vector and the cDNA of claim 17.
20. A Host Cell comprising the Plasmid of claim 19.
21. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-1(E232K).
22. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 21.
- 15 23. A Plasmid comprising a Vector and the cDNA of claim 21.
24. A Host Cell comprising the Plasmid of claim 23.
25. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-2(G285K).
- 20 26. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 25.
27. A Plasmid comprising a Vector and the cDNA of claim 25.
28. A Host Cell comprising the Plasmid of claim 27.

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29. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hPPR1(L239K).
30. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 29.
- 5 31. A Plasmid comprising a Vector and the cDNA of claim 29.
32. A Host Cell comprising the Plasmid of claim 31.
33. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hG2A(K232A).
34. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 33.
- 10 35. A Plasmid comprising a Vector and the cDNA of claim 33.
36. A Host Cell comprising the Plasmid of claim 35.
37. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hRUP3(L224K).
- 15 38. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 37.
39. A Plasmid comprising a Vector and the cDNA of claim 37.
40. A Host Cell comprising the Plasmid of claim 39.
41. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hRUP5(A236K).
- 20 42. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 41.
43. A Plasmid comprising a Vector and the cDNA of claim 41.

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44. A Host Cell comprising the Plasmid of claim 42.
45. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hRUP6(N267K)
46. A non-endogenous version of a human G protein-coupled receptor encoded by the
5 cDNA of claim 45.
47. A Plasmid comprising a Vector and the cDNA of claim 45.
48. A Host Cell comprising the Plasmid of claim 47.
49. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hRUP7(A302K).
- 10 50. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 49.
51. A Plasmid comprising a Vector and the cDNA of claim 49.
52. A Host Cell comprising the Plasmid of claim 51.
53. A cDNA encoding a non-endogenous, constitutively activated version of a human
15 G protein-coupled receptor comprising hCHN4(V236K).
54. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 53.
55. A Plasmid comprising a Vector and the cDNA of claim 53.
56. A Host Cell comprising the Plasmid of claim 55.
- 20 57. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hMC4(A244K).
58. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 57.

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59. A Plasmid comprising a Vector and the cDNA of claim 57.
60. A Host Cell comprising the Plasmid of claim 60.
61. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN3(S284K).
- 5 62. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 61.
63. A Plasmid comprising a Vector and the cDNA of claim 61.
64. A Host Cell comprising the Plasmid of claim 63.
65. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN6(L352K).
- 10 66. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 65.
67. A Plasmid comprising a Vector and the cDNA of claim 65.
68. A Host Cell comprising the Plasmid of claim 67.
- 15 69. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN8(N235K).
70. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 69.
71. A Plasmid comprising a Vector and the cDNA of claim 69.
- 20 72. A Host Cell comprising the Plasmid of claim 71.
73. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hH9(F236K).
74. A non-endogenous version of a human G protein-coupled receptor encoded by the

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cDNA of claim 73.

75. A Plasmid comprising a Vector and the cDNA of claim 73.

76. A Host Cell comprising the Plasmid of claim 74.

77. A cDNA encoding a non-endogenous, constitutively activated version of a human

5 G protein-coupled AT1 receptor selected from the group consisting of:

hAT1(F239K); hAT1(N111A); hAT1(AT2K255IC3); and hAT1(A243+).

78. A non-endogenous version of a human G protein-coupled receptor encoded by a

cDNA of claim 77.

79. A Plasmid comprising a Vector and the cDNA of claim 77.

10 80. A Host Cell comprising the Plasmid of claim 79.

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	145		150		155		160									
	Phe	His	Pro	His	Phe	Val	Leu	Thr	Leu	Ser	Cys	Val	Gly	Phe	Phe	Pro
					165					170						175
5	Ala	Met	Leu	Leu	Ph	Val	Phe	Phe	Tyr	Cys	Asp	Met	Leu	Lys	Ile	Ala
				180					185					190		
	Ser	Met	His	Ser	Gln	Gln	Ile	Arg	Lys	Met	Glu	His	Ala	Gly	Ala	Met
			195					200					205			
	Ala	Gly	Gly	Tyr	Arg	Ser	Pro	Arg	Thr	Pro	Ser	Asp	Phe	Lys	Ala	Leu
		210					215					220				
10	Arg	Thr	Val	Ser	Val	Leu	Ile	Gly	Ser	Phe	Ala	Leu	Ser	Trp	Thr	Pro
	225					230					235					240
	Phe	Leu	Ile	Thr	Gly	Ile	Val	Gln	Val	Ala	Cys	Gln	Glu	Cys	His	Leu
				245						250					255	
15	Tyr	Leu	Val	Leu	Glu	Arg	Tyr	Leu	Trp	Leu	Leu	Gly	Val	Gly	Asn	Ser
			260						265					270		
	Leu	Leu	Asn	Pro	Leu	Ile	Tyr	Ala	Tyr	Trp	Gln	Lys	Glu	Val	Arg	Leu
			275					280					285			
	Gln	Leu	Tyr	His	Met	Ala	Leu	Gly	Val	Lys	Lys	Val	Leu	Thr	Ser	Phe
		290					295					300				
20	Leu	Leu	Phe	Leu	Ser	Ala	Arg	Asn	Cys	Gly	Pro	Glu	Arg	Pro	Arg	Glu
	305					310					315					320
	Ser	Ser	Cys	His	Ile	Val	Thr	Ile	Ser	Ser	Ser	Glu	Phe	Asp	Gly	
					325				330					335		

(10) INFORMATION FOR SEQ ID NO:9:

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1413 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 30 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATGGACACTA	CCATGGAAGC	TGACCTGGGT	GCCACTGGCC	ACAGGCCCCCG	CACAGAGCTT	60
GATGATGAGG	ACTCCTACCC	CCAAGGTGGC	TGGGACACGG	TCTTCCTGGT	GGCCCTGCTG	120
CTCCTTGGGC	TGCCAGCCAA	TGGGTTGATG	GCGTGGCTGG	CCGGCTCCCA	GGCCCGGCAT	180
GGAGCTGGCA	CGCGTCTGGC	GCTGCTCCTG	CTCAGCCTGG	CCCTCTCTGA	CTTCTTGTTT	240

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CTGGCAGCAG CGGCCTTCCA GATCCTAGAG ATCCGGCATG GGGGACACTG GCCGCTGGGG 300
 ACAGCTGCCT GCCGCTTCTA CTACTTCCTA TGGGGCGTGT CCTACTCCTC CGGCCTCTTC 360
 CTGCTGGCCG CCTCAGCCT CGACCGCTGC CTGTGGCGC TGTGCCACA CTGGTACCCT 420
 GGGCACC GCC CAGTCCGCCT GCGCTCTGTG GTCTGCGCCG GTGTCTGGGT GCTGGCCACA 480
 5 CTCTTCAGCG TGCCCTGGCT GGTCTTCCCC GAGGCTGCCG TCTGGTGGTA CGACCTGGTC 540
 ATCTGCCTGG ACTTCTGGGA CAGCGAGGAG CTGTGCTGA GGATGCTGGA GGTCTGGGG 600
 GGCTTCCTGC CTTCCTCCT GTGCTCGTC TGCCACGTGC TCACCCAGGC CACAGCCTGT 660
 CGCAGCTGCC ACCGCCAACA GCAGCCCGCA GCCTGCCGGG GCTTCGCCCC TGTGGCCAGG 720
 ACCATTCTGT CAGCCTATGT GGTCTGAGG CTGCCCTACC AGCTGGCCCA GCTGCTCTAC 780
 10 CTGGCCTTCC TGTGGGACGT CTACTCTGGC TACCTGCTCT GGGAGGCCCT GGTCTACTCC 840
 GACTACCTGA TCCTACTCAA CAGCTGCCTC AGCCCCCTTC TCTGCCTCAT GGCCAGTGCC 900
 GACCTCCGGA CCTGCTGCG CTCCGTGCTC TCGTCTTCG CGGCAGCTCT CTGCGAGGAG 960
 CGGCCGGGCA GCTTCACGCC CACTGAGCCA CAGACCCAGC TAGATTCTGA GGGTCCAACT 1020
 CTGCCAGAGC CGATGGCAGA GGCCAGTCA CAGATGGATC CTGTGGCCCA GCCTCAGGTG 1080
 15 AACCCACAC TCCAGCCAG ATCGGATCCC ACAGCTCAGC CACAGCTGAA CCCTACGGCC 1140
 CAGCCACAGT CGGATCCCAC AGCCAGCCA CAGCTGAACC TCATGGCCCA GCCACAGTCA 1200
 GATTCTGTGG CCCAGCCACA GGCAGACACT AACGTCCAGA CCCCTGCACC TGCTGCCAGT 1260
 TCTGTGCCCA GTCCCTGTGA TGAAGCTTCC CCAACCCCAT CCTCGCATCC TACCCAGGG 1320
 GCCCTTGAGG ACCCAGCCAC ACCTCCTGCC TCTGAAGGAG AAAGCCCCAG CAGCACCCCG 1380
 20 CCAGAGGCGG CCGCGGGCGC AGGCCCCAG TGA 1413

(11) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 468 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

30 Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro
 1 5 10 15

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Arg Thr Glu Leu Asp Asp Glu Asp Ser Tyr Pro Gln Gly Gly Trp Asp
 20 25 30
 Thr Val Phe Leu Val Ala Leu Leu Leu Gly Leu Pro Ala Asn Gly
 35 40 45
 5 Leu Met Ala Trp Leu Ala Gly Ser Gln Ala Arg His Gly Ala Gly Thr
 50 55 60
 Arg Leu Ala Leu Leu Leu Ser Leu Ala Leu Ser Asp Phe Leu Phe
 65 70 75 80
 10 Leu Ala Ala Ala Ala Phe Gln Ile Leu Glu Ile Arg His Gly Gly His
 85 90 95
 Trp Pro Leu Gly Thr Ala Ala Cys Arg Phe Tyr Tyr Phe Leu Trp Gly
 100 105 110
 Val Ser Tyr Ser Ser Gly Leu Phe Leu Leu Ala Ala Leu Ser Leu Asp
 115 120 125
 15 Arg Cys Leu Leu Ala Leu Cys Pro His Trp Tyr Pro Gly His Arg Pro
 130 135 140
 Val Arg Leu Pro Leu Trp Val Cys Ala Gly Val Trp Val Leu Ala Thr
 145 150 155 160
 20 Leu Phe Ser Val Pro Trp Leu Val Phe Pro Glu Ala Ala Val Trp Trp
 165 170 175
 Tyr Asp Leu Val Ile Cys Leu Asp Phe Trp Asp Ser Glu Glu Leu Ser
 180 185 190
 Leu Arg Met Leu Glu Val Leu Gly Gly Phe Leu Pro Phe Leu Leu Leu
 195 200 205
 25 Leu Val Cys His Val Leu Thr Gln Ala Thr Arg Thr Cys His Arg Gln
 210 215 220
 Gln Gln Pro Ala Ala Cys Arg Gly Phe Ala Arg Val Ala Arg Thr Ile
 225 230 235 240
 30 Leu Ser Ala Tyr Val Val Leu Arg Leu Pro Tyr Gln Leu Ala Gln Leu
 245 250 255
 Leu Tyr Leu Ala Phe Leu Trp Asp Val Tyr Ser Gly Tyr Leu Leu Trp
 260 265 270
 Glu Ala Leu Val Tyr Ser Asp Tyr Leu Ile Leu Leu Asn Ser Cys Leu
 275 280 285
 35 Ser Pro Phe Leu Cys Leu Met Ala Ser Ala Asp Leu Arg Thr Leu Leu
 290 295 300
 Arg Ser Val Leu Ser Ser Phe Ala Ala Ala Leu Cys Glu Glu Arg Pro

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	305		310		315		320
	Gly Ser Phe Thr Pro Thr Glu Pro Gln Thr Gln Leu Asp Ser Glu Gly						
		325			330		335
5	Pro Thr Leu Pro Glu Pro Met Ala Glu Ala Gln Ser Gln Met Asp Pro						
		340			345		350
	Val Ala Gln Pro Gln Val Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro						
		355			360		365
	Thr Ala Gln Pro Gln Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro						
		370			375		380
10	Thr Ala Gln Pro Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser						
		385			390		395
	Val Ala Gln Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala						
			405		410		415
15	Ala Ser Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser						
		420			425		430
	Ser His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala						
		435			440		445
	Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro Gly						
		450			455		460
20	Ala Gly Pro Thr						
	465						

(12) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
- 25 (A) LENGTH: 1248 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

30	ATGTCAGGGA TGGAAAACT TCAGAAATGCT TCCTGGATCT ACCAGCAGAA ACTAGAAGAT	60
	CCATTCCAGA AACACCTGAA CAGCACCGAG GAGTATCTGG CCTTCCTCTG CGGACCTCGG	120
	CGCAGCCACT TCTTCCTCCC CGTGTCTGTG GTGTATGTGC CAATTTTGTG GGTGGGGGTC	180
	ATTGGCAATG TCCTGGTGTG CCTGGTGATT CTGCAGCACC AGGCTATGAA GACGCCCCACC	240
	AACTACTACC TCTTCAGCCT GCGGTCTCT GACCTCCTGG TCCTGCTCCT TGAATGCCC	300